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(54) Title: QUATERNARY AMMONIUM SALTS OF FUSED HETEAROMATIC AMINES AS NOVEL MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS

(57) Abstract: Novel derivatives of cyclic amines, pharmaceutical compositions, processes for their preparation, and use thereof in treating muscarinic acetylcholine receptor mediated diseases are provided.

Quaternary Ammonium Salts of Fused Hetearomatic Amines as Novel Muscarinic Acetylcholine Receptor Antagonists

FIELD OF THE INVENTION

This invention relates to novel derivatives of cyclic amines, pharmaceutical compositions, processes for their preparation, and use thereof in treating muscarinic acetylcholine receptors mediated diseases.

BACKGROUND OF THE INVENTION

Acetylcholine released from cholinergic neurons in the peripheral and central nervous systems affects many different biological processes through interaction with two major classes of acetylcholine receptors – the nicotinic and the muscarinic acetylcholine receptors. Muscarinic acetylcholine receptors (mAChRs) belong to the superfamily of G-protein coupled receptors that have seven transmembrane domains. There are five subtypes of mAChRs, termed M_1-M_5, and each is the product of a distinct gene. Each of these five subtypes displays unique pharmacological properties. Muscarinic acetylcholine receptors are widely distributed in vertebrate organs, and these receptors can mediate both inhibitory and excitatory actions. For example, in smooth muscle found in the airways, bladder and gastrointestinal tract, M_3 mAChRs mediate contractile responses. For review, please see {Brown 1989 247 /id}.

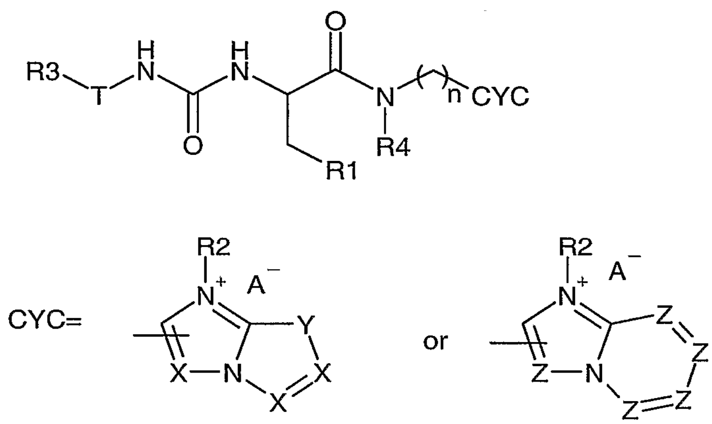
Muscarinic acetylcholine receptor dysfunction has been noted in a variety of different pathophysiological states. For instance, in asthma and chronic obstructive pulmonary disease (COPD), inflammatory conditions lead to loss of inhibitory M_2 muscarinic acetylcholine autoreceptor function on parasympathetic nerves supplying the pulmonary smooth muscle, causing increased acetylcholine release following vagal nerve stimulation. This mAChR dysfunction results in airway hyperreactivity mediated by increased stimulation of M_3 mAChRs{Costello, Evans, et al. 1999 72 /id}{Minette, Lammers, et al. 1989 248 /id}. Similarly, inflammation of the gastrointestinal tract in inflammatory bowel disease (IBD) results in M_3 mAChR-mediated hypermotility {Oprins, Meijer, et al. 2000 245 /id}. Incontinence due to bladder hypercontractility has also been demonstrated to be mediated through increased stimulation of M_3 mAChRs {Hegde & Eglen 1999 251 /id}. Thus the identification of subtytpe-selective mAChR antagonists may be useful as therapeutics in these mAChR-mediated diseases.

Despite the large body of evidence supporting the use of anti-muscarinic receptor therapy for treatment of a variety of disease states, relatively few anti-muscarinic

compounds are in use in the clinic. Thus, there remains a need for novel compounds that are capable of causing blockade at M_3 mAChRs. Conditions associated with an increase in stimulation of M_3 mAChRs, such as asthma, COPD, IBD and urinary incontinence would benefit by compounds that are inhibitors of mAChR binding.

SUMMARY OF THE INVENTION

This invention relates to compounds of Formula I



(I)

wherein,

Y is S, O; or NR4

X is N, or CR5, provided that the number of N at the X value cannot exceed 2;

Z is N, or CR5, provided that the number of N at the Z value cannot exceed 3;

N is and integer from 0 to 3;

A^- is selected from the group consisting of halo, CF_3COO^-, mesylate, tosylate, and any other pharmaceutically acceptable counter ion;

R1 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, C_3-C_8 alkenyl, unsubstituted or substituted phenyl, or unsubstituted and substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

T is selected from the group consisting of thiophene, furan, thiazole, isothiazole, pyrrole, imidazole, pyrazole and para-substituted phenyl which may be substituted by one or more

radical selected from the group consisting of C_1-C_3 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_4 branched or unbranched alkyl, C_3-C_8 cycloalkyl, and C_3-C_8 cycloalkyl lower alkyl or phenyl;

R2 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl and unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, and C_1-C_3 branched or unbranched alkyl;

R3 is selected from the group consisting of COR6, COOR6, OSO_2R6, $N(R7)SO_2R6$, CONR6R7, NR6R7, OCOR6, OCONR6R7, NHCOR6, N(R7)COR6, NHCOOR6 and NHCONR6R7;

R4 is selected from the group consisting of hydrogen, C1-C3 alkyl and allyl;

R5 is selected from the following groupconsisting of hydrogen, C1-C3 alkyl, C1-C3 alkenyl, , halo, NR4, OR4, CN, NO_2, and trifluoromethyl;

R6 is selected from the group consisting of substituted or unsubstituted C_1-C_8 branched or unbranched alkyl, C_3-C_{12} cycloalkyl, C_3-C_{12} cycloalkenyl, C_3-C_8 cycloalkyl lower alkyl, C_3-C_8 alkenyl, phenyl, and phenyl C1-C3 lower alkyl wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, nitro, trifluoromethyl, and C_1-C_3 branched or unbranched alkyl; and

R7 is selected from the group consisting of: hydrogen, C1-C4 alkyl and allyl.

The present invention includes all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds that release the active parent drug according to Formula I **in vivo**. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Inventive compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric

form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

The meaning of any substituent at any one occurrence in Formula I or any subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of the present invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in **Eur. J. Biochem.**, 158, 9 (1984).

The term "C_1-C_8 alkyl" and "C_1-C_6 alkyl" is used herein includes both straight or branched chain radicals of 1 to 6 or 8 carbon atoms. By example this term includes, but is not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, *tert*-butyl, pentyl, hexyl, heptyl, octyl and the like. "Lower alkyl" has the same meaning as C_1-C_8 alkyl.

Herein "C_1-C_8 alkoxy" includes straight and branched chain radicals of the likes of $-O-CH_3$, $-O-CH_2CH_3$, and the n-propoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy, *tert*-butoxy, pentoxy, and hexoxy, and the like.

"C_3-C_8-cycloalkyl" as applied herein is meant to include substituted and unsubstituted cyclopropane, cyclobutane, cyclopentane and cyclohexane, and the like.

"Halogen" or "halo" means F, Cl, Br, and I.

The preferred compounds of Formula I include those compounds wherein,

Y is S, O; or NR4

X is N, or CR5, provided that the number of N at the X value cannot exceed 2;

Z is N, or CR5, provided that the number of N at the Z value cannot exceed 3;

n is an integer from 0 to 3;

A^- is selected from the group consisting of halo, CF_3COO^-, mesylate, tosylate, or any other pharmaceutically acceptable counter ion;

R1 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, C_3-C_8 alkenyl, unsubstituted or substituted phenyl, and unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched

or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

T is selected from the group consisting of thiophene, furan, thiazole, isothiazole, pyrrole, imidazole, pyrazole and para-substituted phenyl which may be substituted by radicals selected from the group consisting of C_1-C_3 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_4 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl and phenyl;

R2 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl and unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, and C_1-C_3 branched or unbranched alkyl;

R3 is selected from the group consisting of COR6, COOR6, OSO_2R6, $N(R7)SO_2R6$, CONR6R7, NR6R7, OCOR6, OCONR6R7, NHCOR6, N(R7)COR6, NHCOOR6 and NHCONR6R7;

R4 is selected from the group consisting of hydrogen, C1-C3 alkyl and allyl;

R5 is selected from the group consisting of hydrogen, C1-C3 alkyl, C1-C3 alkenyl, , halo, NR4, OR4, CN, NO_2, and trifluoromethyl;

R6 is selected from the group consisting of substituted or unsubstituted C_1-C_8 branched or unbranched alkyl, C_3-C_{12} cycloalkyl, C_3-C_{12} cycloalkenyl, C_3-C_8 cycloalkyl lower alkyl, C_3-C_8 alkenyl, phenyl, and phenyl C1-C3 lower alkyl wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, nitro, trifluoromethyl, and C_1-C_3 branched or unbranched alkyl;

R7 is selected from the group consisting of: hydrogen, C1-C4 alkyl and allyl.

More preferred are those compounds where:

Y is S or O

X is CR5;

Z is CR5;

N is 1 or 2;

A^- is selected from the group consisting of halo, CF_3COO^-, mesylate, tosylate, and any other pharmaceutically acceptable counter ion;

R1 is selected from the group consisting of unsubstituted or substituted phenyl wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

T is selected from the group consisting of thiophene, furan, and para-substituted phenyl which may be substituted by radicals selected from the group consisting of C_1-C_3 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_4 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl and phenyl;

R2 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl and unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, and C_1-C_3 branched or unbranched alkyl;

R3 is selected from the group consisting of COOR6, OSO_2R6, $N(R7)SO_2R6$, and CONR6R7,;

R4 is selected from the group consisting of hydrogen, C1-C3 alkyl and allyl;

R5 is selected from the group consisting of hydrogen, C1-C3 alkyl, C1-C3 alkenyl, , halo, NR4, OR4, CN, NO_2, and trifluoromethyl;

R6 is selected from the group consisting of substituted or unsubstituted C_1-C_8 branched or unbranched alkyl, C_3-C_{12} cycloalkyl, C_3-C_{12} cycloalkenyl, C_3-C_8 cycloalkyl lower alkyl, C_3-C_8 alkenyl, phenyl, or phenyl C1-C3 lower alkyl wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, nitro, trifluoromethyl, and C_1-C_3 branched or unbranched alkyl;

R7 is selected from the group consisting of hydrogen, C1-C3 alkyl and allyl.

Even more preferred are those compounds where:

Y is S;

X is CR5;

Z is CR5;

N is 1;

A^- is selected from the group consisting of halo, CF_3COO^-, mesylate, tosylate, and any other pharmaceutically acceptable counter ion;

R1 is selected from the group consisting of unsubstituted or substituted phenyl wherein, when substituted, a group is substituted at the meta or para position by one radical selected from the group consisting of C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, nitro, trifluoromethyl, and C_1-C_3 branched or unbranched alkyl;

T is selected from thiophene or para-substituted phenyl;

R2 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl and unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of halo, methoxy, nitro, cyano, trifluoromethyl, and C_1-C_2 alkyl;

R3 is selected from the group consisting of COOR6, OSO_2R6, and $N(R7)SO_2R6$;

R4 is hydrogen;

R5 is hydrogen;

R6 is selected from the group consisting of substituted or unsubstituted C_1-C_8 branched or unbranched alkyl, C_3-C_9 cycloalkyl, C_3-C_9 cycloalkenyl, C_3-C_8 cycloalkylmethyl, and C_3-C_8 alkenyl;

The preferred compounds are selected from the group consisting of:

N-[({5-[(cyclopentyloxy)carbonyl]-2-thienyl}amino)carbonyl]-*N*-[(2,7-dimethylimidazo[2,1-*b*][1,3]thiazol-7-ium-6-yl)methyl]-L-tyrosinamide trifluoroacetate;

N-[({5-[(cyclohexyloxy)carbonyl]-2-thienyl}amino)carbonyl]-*N*-[(2,7-dimethylimidazo[2,1-*b*][1,3]thiazol-7-ium-6-yl)methyl]-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)amino]sulfonyl}phenyl)amino]carbonyl}-*N*-{[2-methyl-7-(phenylmethyl)imidazo[2,1-*b*][1,3]thiazol-7-ium-6-yl]methyl}-L-tyrosinamide trifluoroacetate;

N-[(2,7-dimethylimidazo[2,1-*b*][1,3]thiazol-7-ium-6-yl)methyl]-*N*-{[(4-{[(1-methylethyl)amino]sulfonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

4-[(2*S*)-3-{[(1,7-dimethylimidazo[1,2-*a*]pyridin-1-ium-2-yl)methyl]amino}-2-({[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}amino)-3-oxopropyl]benzenolate trifluoroacetate;

N-[({5-[(cyclohexyloxy)carbonyl]-2-thienyl}amino)carbonyl]-*N*-{[2-methyl-7-(2-naphthalenylmethyl)-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl]methyl}-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-[(7-methylimidazo[2,1-*b*][1,3]thiazol-7-ium-6-yl)methyl]-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-[(7-methylimidazo[2,1-*b*][1,3]thiazol-7-ium-6-yl)methyl]-L-tyrosinamide trifluoroacetate;

N-[(2,7-dimethylimidazo[2,1-*b*][1,3]thiazol-7-ium-6-yl)methyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-({2-methyl-7-[(2-methylphenyl)methyl]-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-L-tyrosinamide trifluoroacetate;

N-({7-[(4-bromophenyl)methyl]-2-methyl-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino] carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(7-{[4-(1,1-dimethylethyl)phenyl]methyl}-2-methyl-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl)methyl]-*N*-{[(4-{[(1-methylethyl)oxy] carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-({2-methyl-7-[(4-methylphenyl)methyl]-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-L-tyrosinamide trifluoroacetate;

N-({7-[(2-fluorophenyl)methyl]-2-methyl-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino] carbonyl}-L-tyrosinamide trifluoroacetate;

N-({7-[(3-fluorophenyl)methyl]-2-methyl-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino] carbonyl}-L-tyrosinamide trifluoroacetate;

N-({7-[(4-fluorophenyl)methyl]-2-methyl-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino] carbonyl}-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-[(2-methyl-7-{[3-(trifluoromethyl)phenyl]methyl}-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl)methyl]-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-[(2-methyl-7-{[4-(trifluoromethyl)phenyl]methyl}-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl)methyl]-L-tyrosinamide trifluoroacetate;

N-({7-[(3-cyanophenyl)methyl]-2-methyl-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino] carbonyl}-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-{[2-methyl-7-(2-naphthalenylmethyl)-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl]methyl}-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-({2-methyl-7-[(2-nitrophenyl)methyl]-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-({2-methyl-7-[(3-nitrophenyl)methyl]-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-({2-methyl-7-[(4-nitrophenyl)methyl]-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-[(2-methyl-7-{[2-(trifluoromethyl)phenyl]methyl}-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl)methyl]-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-{[2-methyl-7-({4-[(trifluoromethyl)oxy]phenyl}methyl)-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl]methyl}-L-tyrosinamide trifluoroacetate

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl);amino]carbonyl}-*N*-{[2-methyl-7-({3-[(trifluoromethyl)oxy]phenyl}methyl)-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl]methyl}-L-tyrosinamide trifluoroacetate;

N-[(2,7-dimethylimidazo[2,1-*b*][1,3]thiazol-7-ium-5-yl)methyl]-*N*-({[5-({[3-(phenyloxy)propyl]oxy}carbonyl)-2-thienyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate; and

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-[(2-methyl-7-{[3-(methyloxy)phenyl]methyl}-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl)methyl]-L-tyrosinamide trifluoroacetate; or a pharmaceutically acceptable salt.

Methods of Preparation

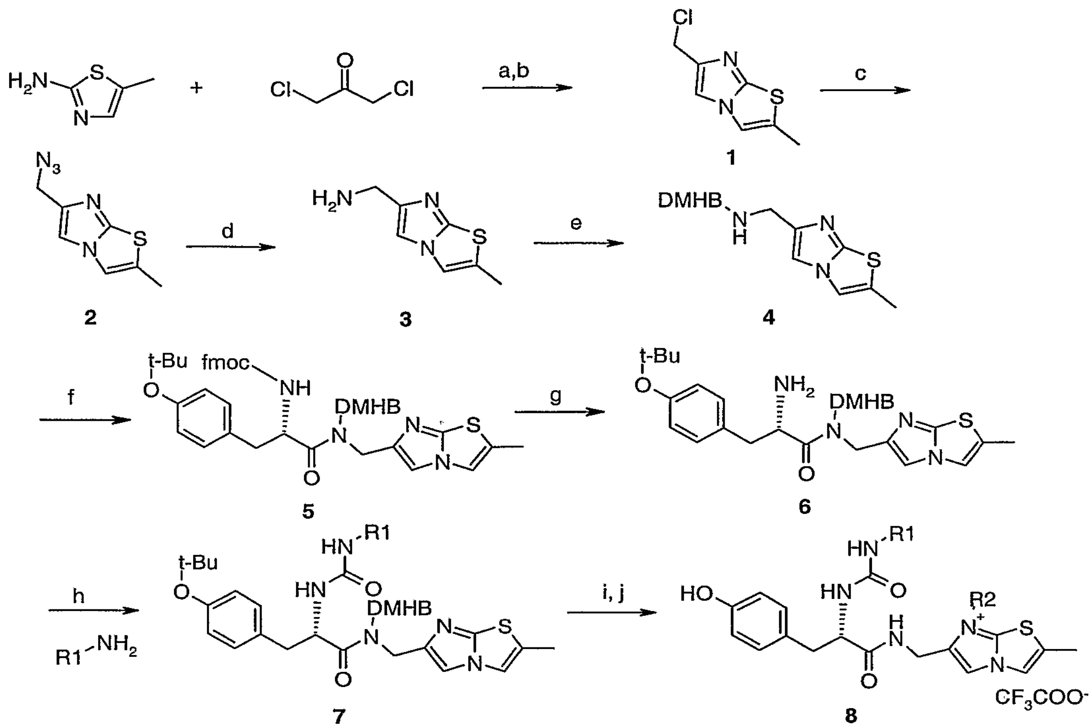
Preparation

The compounds of Formula (I) may be obtained by applying synthetic procedures, some of which are illustrated in the Schemes below. The synthesis provided for these Schemes is applicable for producing compounds of Formula (I) having a variety of different R1, R3, R4, R5 and R6, which are reacted, employing substituents which are suitable protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. While some Schemes are shown with specific compounds, this is merely for illustration purpose only.

Preparation 1

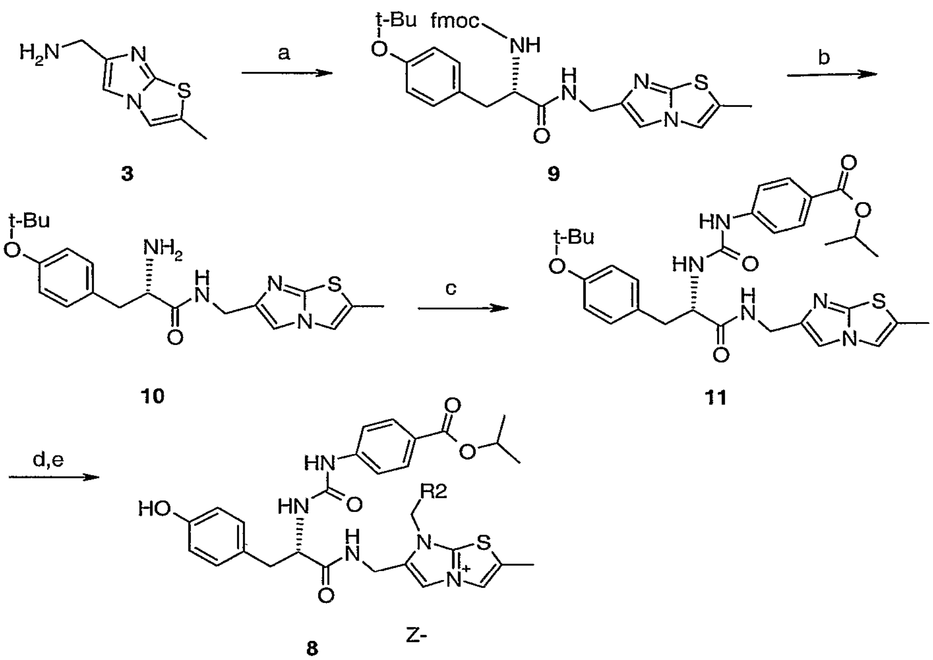
Compounds of formula **8** can be prepared according to the general schemes (1, 2 and 3) depicted below. Scheme 1 showed the solid phase synthesis. 2-Amino-5-methylthiazole was treated with sodium bromide and dichloroacetone to provide 6-(chloromethyl)-2-methylimidazo[2,1-*b*][1,3]thiazole **1** , which was reacted with sodium azide to form 6-(azidomethyl)-2-methylimidazo[2,1-*b*][1,3]thiazole **2**. The azide **2** was converted to amine **3** by hydrogenation via 10% palladium on carbon. Resin-bound amine **4** was prepared by reductive amination of 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) with amine **3**. Reaction of **4** with Fmoc-protected amino acid, followed by removal of the protecting group, provided resin-bound intermediate **6**. The amines were coupled with resin-bound intermediate **6** to afford the corresponding resin-bound ureas **7**, which were treated with alkyl halides to form the corresponding quaternary ammonium salts. The resin was then cleaved by 50% trifluoroacetic acid in dichloromethane to afford targeted compounds **8** (Scheme 1). Scheme 2 and 3 showed the synthesis of formula **8** compounds using solution phase synthesis. The sequence and reaction conditions are similar.

Scheme 1



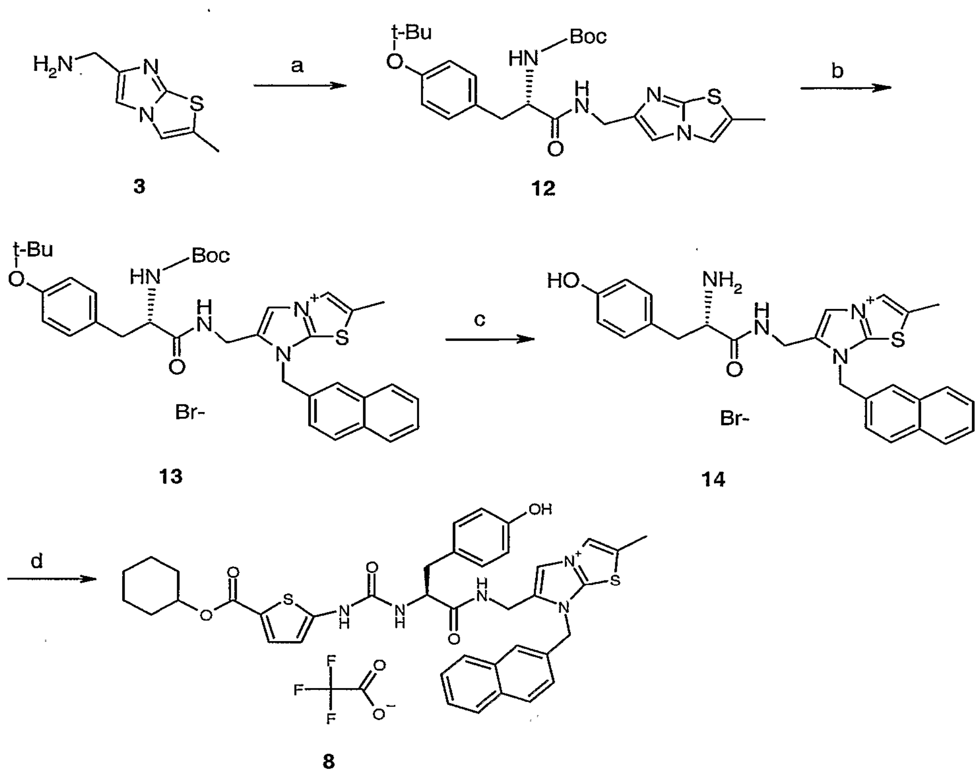
Conditions: a) NaBr, rt,14hrs. b) 110 ^{o}C for 1hrs. c) NaN_3, DMSO, 65 ^{o}C d) 10% palladium on carbon, H_2, rt ; e) 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin), $Na(OAc)_3BH$, diisopropylethylamine, 10% acetic acid in 1-methyl-2-pyrrolidinone, rt; f) Fmoc-protected amino acids, 1,3-diisopropylcarbodiimide, 1-hydroxy-7-azabenzotriazole, 1-methyl-2-pyrrolidinone, rt; g) 20% piperidine in 1-methyl-2-pyrrolidinone, rt; h) 4-nitrobenzene chloroformate, $R1NH_2$, diisopropylethylamine, N,N-dimethyl formamide, dichloromethane, rt; i) R_2Z, acetonitrile, rt; j) 50% trifluoroacetic acid in dichloromethane, rt.

Scheme 2



Conditions: a) Fmoc-protected amino acids, 1,3-diisopropylcarbodiimide, o-(7-azabenxotriazol-1-yl)-N,N,N',N'-tetramethyluronium, DMF, rt; b) 20% piperidine in 1-methyl-2-pyrrolidinone, rt; c) 1-methylethyl 4-isocyanatobenzoate , pyridine, ethyl acetate, rt; d) R_2Z, acetonitrile, rt; e) 40% trifluoroacetic acid in dichloromethane, rt.

Scheme 3



Conditions: a) Boc-Tyr(Butyl)-OH, 1,3-diisopropylcarbodiimide, o-(7-azabenxotriazol-1-yl)-N,N,N',N'-tetramethyluronium, DMF, rt; b) bromethyl naphthalene, acetonitrile, chloroform, 170 ^{O}C; c) trifluoroacetic acid in dichloromethane, rt; d) cyclohexyl 5-amino-2-thiophenecarboxylate, 4-nitrobenzene chloroformate, diisopropylethylamine, N,N-dimethyl formamide, dichloromethane, rt.

SYNTHETIC EXAMPLES

The following examples are provided as illustrative of the present invention but not limiting in any way:

Example 1

Preparation of *N*-[({5-[(cyclohexyloxy)carbonyl]-2-thienyl}amino) carbonyl]-*N*-[(2,7-dimethylimidazo[2,1-*b*][1,3]thiazol-7-ium-5-yl)methyl]-L-tyrosinamide trifluoroacetate

Sodium bromide (7.2 g, 69.98 mmol) and dichloroacetone (4.88 g, 38.43 mmol) were added to 2-Amino-5-methylthiazole (4.0 g, 35.04 mmol) in ethyl acetate (140 mL). The reaction mixture was stirred at room temperature for 14 hours. Significant amount of

solid precipitated out and filtered off. The solid was dissolved in acetic acid (250 mL) and heated to 110 ^{O}C for 1 hour. The reaction mixture was cooled to room temperature overnight. Significant amount of solid precipitated out again. The solid was filtered off, washed with acetic acid (75 mL), acetone (200 mL), diethyl ether (200 mL) and air dried overnight to afford 6-(chloromethyl)-2-methylimidazo[2,1-*b*][1,3]thiazole **1** (4.86 g, 74.2%).

LC/MS 151.2 $[M+H-Cl]^+$ Rt, 0.72min.

6-(Chloromethyl)-2-methylimidazo[2,1-*b*][1,3]thiazole **1** (4.47 g, 23.82 mmol) was dissolved in DMSO (50 mL). Sodium azide (1.55 g, 23.82 mmol) was added. The reaction mixture was heated to 65 ^{O}C overnight. Water (200 mL) was added after the reaction mixture was cooled to room temperature. The mixture was extracted with ethyl acetate (3x 150 mL). The combined organic phase was washed with brine(150 mL), dried over $MgSO_4$, concentrated and purified with combiflash eluting with (100% methylene chloride to 5:95% methylene chloride verse ethyl acetate) to afford 6-(azidomethyl)-2-methylimidazo[2,1-*b*][1,3]thiazole **2** (1.64 g, 35%).

LCMS (ESI) 194.0 $[M+H]^+$ Rt, 1.24 min.

6-(Azidomethyl)-2-methylimidazo[2,1-*b*][1,3]thiazole **2** (1.64 g, 8.45 mmol) was dissolved in methanol (50 mL). 10% Palladium on carbon (0.42 g) was added. The reaction mixture was hydrogenated at 1 atmosphere overnight to afford 1-(2-methylimidazo[2,1-*b*][1,3]thiazol-6-yl)methanamine **3** (1.30 g, 97%) after filtration and concentration.

LCMS (ESI) 335.2 $[2M+H]^+$ Rt, 1.16 min.

To a mixture of 5.78 g (8.68 mmol, 1.50 mmol/g) of 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) in 100 mL of 10% acetic acid in anhydrous 1-methyl-2-pyrrolidinone was added of 1-(2-methylimidazo[2,1-*b*][1,3]thiazol-6-yl)methanamine **3** (2.9 g, 17.36 mmol)and 6.05 mL (34.72 mmol) of diisopropylethyl amine, followed by addition of sodium triacetoxyborohydride (7.38 g, 34.72 mmol). After the resulting mixture was shaken at rt for 72 h, the resin was washed with DMF (3 x 250 mL), CH_2Cl_2/MeOH (1:1, 3 x 250 mL) and MeOH (3 x 250 mL). The resulting resin was dried in vacuum oven at 35 ^{O}C for 24 h.

To a mixture of the above resin (8.68 mmol) in 100 mL of anhydrous 1-methyl-2-pyrrolidinone was added 11.6 g (25.14 mmol) of Fmoc-Try(tBu)-OH and 1.18 g (8.68 mmol) of 1-hydroxy-7-azabenzotriazole, followed by addition of 5.51 mL (34.72 mmol) of 1,3-diisopropylcarbodiimide. After the resulting mixture was shaken at rt for 24 h, the

resin was washed with DMF (3 x 50 mL), CH_2Cl_2/MeOH (1:1, 3 x 50 mL) and MeOH (3 x 50 mL). The resulting resin **5** was dried in vacuum oven at 35 ^{o}C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 553.6 $[M+H-tBu]^+$. Rt, 1.78 min.

The above resin **5** (8.68 mmol) was treated with 100 mL of 20% piperidine in anhydrous 1-methyl-2-pyrrolidinone solution. After the mixture was shaken at room temperature for 15 min, the solution was drained and another 100 mL of 20% piperidine in anhydrous 1-methyl-2-pyrrolidinone solution was added. The mixture was shaken at rt for another 15 min. The solution was drained and the resin was washed with DMF (3 x 50 mL), CH_2Cl_2/MeOH (1:1, 3 x 50 mL) and MeOH (3 x 50 mL). The resulting resin **6** was dried in vacuum oven at 35 ^{o}C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 331 $[M+H-tBu]^+$ Rt, 1.06 min.

5-Nitro-2-thiophenecarboxylic acid (2.8 g, 16 mmol) was suspended in methylene chloride (50 mL). Oxalyl chloride in methylene chloride (2.0 M, 32.3 mL) was added at room temperature followed by one drop of dimethyl formamide (0.1 mL). The reaction mixture was stirred at RT for 1 hr and concentrated. Methylene chloride (100 mL) was added, concentrated again and redissolved in methylene chloride (60 mL). N, N'-Dimethylaminopyridine (652 mg, 5.33 mmol) , triethyl amine(4.47 mL, 32 mmol) and cyclohexanol (2.54 mL, 24 mmol) were added to reaction mixture and stirred at room temperature overnight. The reaction mixture was filtered through a pad of silica gel (250 g), eluting with methylene chloride. The crude cyclohexyl 5-nitro-2-thiophenecarboxylate was obtained after concentration, which was used in the next step without further purification.

LC/MS (ESI) 256 $[M+H]^+$.

To cyclohexyl 5-nitro-2-thiophenecarboxylate (16 mmol) in ethyl alcohol (50 mL) was added palladium on carbon (10%, 2 g). The reaction mixture was hydrogenated at 15 psi overnight. Cyclohexyl 5-amino-2-thiophenecarboxylate (4 g, 90%) was obtained after filtration and concentration.

LCMS (ESI) 226.2 $[M+H]^+$.

To a mixture of 700 mg (3.11 mmol) cyclohexyl 5-amino-2-thiophenecarboxylate in 10mL of anhydrous dichloromethane was added 627 mg (3.11 mmol) 4-

nitrobezenechloroformate. The reaction mixture was stirred at room temperature for half an hour and concentrated. Diisopropylethylamine (1.09 mL, 6.22 mmol), DMHB resin bound *N*-[(2-methylimidazo[2,1-*b*][1,3]thiazol-6-yl)methyl]-L-tyrosinamide(500 mg, 0.4 mmol) **6** and dimethyl formamide (15 mL) were added to reaction mixture and shaked overnight. The resin was washed with CH_2Cl_2 (3 x 10 mL), CH_2Cl_2/MeOH (1:1, 3 x 10 mL), MeOH (3 x 10 mL) and CH_2Cl_2 (3 x 10mL). The resulting resin was dried in vacuum oven at 35 ^{o}C for 24 h. MS (ESI) 581 $[M+H-tBu]^+$.

To a mixture of the above dry resin (0.4 mmol) in 1 mL of anhydrous acetonitrile was added 0.187 mL (3 mmol) of iodomethane. After the mixture was shaken at rt for 16 h, the resin was washed with DMF (3 x 10 mL), CH_2Cl_2/MeOH (1:1, 3 x 10 mL), MeOH (3 x 10 mL) and CH_2Cl_2 (3x10mL). The resulting resin was dried in vacuum oven at 35 ^{o}C for 24 h. The dry resin was treated with 2 mL of 50% trifluoroacetic acid in dichloromethane at rt for 2h. After the cleavage solution was collected, the resin was treated with another 2 mL of 50% trifluoroacetic acid in dichloromethane at rt for 10min. The combined cleavage solutions were concentrated *in vacuo*. The residue was purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce *N*-[({5-[(cyclohexyloxy)carbonyl]-2-thienyl}amino) carbonyl]-*N*-[(2,7-dimethylimidazo[2,1-*b*][1,3]thiazol-7-ium-5-yl)methyl]-L-tyrosinamide trifluoroacetate (white powder, 5 mg, 2% over 5 steps).

MS (ESI) 596.4 $[M]^+$ Rt, 1.93 min.

Example 2

Preparation of *N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino] carbonyl}-*N*-{[2-methyl-7-(2-naphthalenylmethyl)-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl]methyl}-L-tyrosinamide trifluoroacetate

To 1-(2-methylimidazo[2,1-*b*][1,3]thiazol-6-yl)methanamine **3** (1.43 g, 8.51 mmol) and Fmoc-Try(t-Bu)-OH (4.30 g, 9.36 mmol) dissolved in DMF (60 mL), o-(7-azabenxotriazol-1-yl)-N,N,N',N'-tetramethyluronium (3.56 g, 9.36 mmol) and diisopropylethyl amine (2.96 mL, 17.02 mmol) were added. After the reaction mixture was stirred at room temperature for 3 hrs under argon, the resulting mixture was concentrated and redissolved with ethyl acetate (100 mL) and water (100 mL). The aqueous phase was extracted with ethyl acetate (75 mLx2). The combined organic phase was washed with water (100 mLx3),

brine (100 mL), dried over $MgSO_4$, and concentrated. The residue was purified by combiflash (100 g column, eluting with 10% ethyl acetate/ methylene chloride, 95% ethyl acetate/ methylene chloride) and repurified by combiflash (100 g column, eluting with 5% MeOH/ CH_2Cl_2) to afford *O*-(1,1-dimethylethyl)-*N*-{[(9*H*-fluoren-9-ylmethyl)oxy] carbonyl}-*N*-[(2-methylimidazo[2,1-*b*][1,3]thiazol-6-yl)methyl]-L-tyrosinamide (**9**) (4.48 g, 86%)
LC/MS (ESI) 609.4 $[M+H]^+$ Rt 2.14 min

O-(1,1-dimethylethyl)-*N*-{[(9*H*-fluoren-9-ylmethyl)oxy] carbonyl}-*N*-[(2-methylimidazo[2,1-*b*][1,3]thiazol-6-yl)methyl]-L-tyrosinamide (**9**) (4.48 g, 7.35 mmol) was dissolved in DMF (75 mL). Piperidine (25 mL) was added. The reaction solution was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue was purified by combiflash (40 g column, eluting with 100% methylene chloride, 5% MeOH/ methylene chloride) and repurified by combiflash (40 g column, eluting with 100% methylene chloride, 5% MeOH/ methylene chloride) to afford *O*-(1,1-dimethylethyl)-*N*-[(2-methylimidazo[2,1-*b*][1,3]thiazol-6-yl)methyl]-L-tyrosinamide (**10**) (2.85g, 90%) as a crude product, which was used in the next step without further purification.
LC/MS (ESI) 386.8 $[M+H]^+$ Rt 1.55 min

1-Methylethyl 4-aminobenzoate (0.883 g, 4.94 mmol) was dissolved in dichlorobezene (55 mL) and cooled to zero degree in ice bath. 4 N HCl in dioxane (1.85 mL, 7.4 mmol) was added. The reaction mixture was stirred for 2 hrs. Oxalyl choloride (0.86 mL, 9.86 mmol) was added. The reaction mixture was heated at 145 ^{O}C for 2 hrs to afford 1-methylethyl 4-isocyanatobenzoate in dichlorobezene, which was used in the next step without further purification.

O-(1,1-dimethylethyl)-*N*-[(2-methylimidazo[2,1-*b*][1,3]thiazol-6-yl)methyl]-L-tyrosinamide (**10**) (1.28 g, 3.31 mmol) was dissolved in ethyl acetate (20 mL). Pyridine (1.34 mL, 16.43 mmol) was added. 1-Methylethyl 4-isocyanatobenzoate (4.94 mmol) in dichlorobezene was added slowly. The reaction mixture was stirred at room temperature overnight and running through a pad of silica gel eluting with methylene chloride, followed by 2% NH_4OH/ 8% MeOH/ 90%. The filtrate was concentrated under reduced pressure. The residue was purified by combiflash (120 g column, eluting with 100% methylene chloride, 5% MeOH/ methylene chloride) and repurified by combiflash (40 g column, eluting with ethyl acetate/ methylene chloride 40% to 60%) to afford 1-methylethyl 4-({[((1*S*)-1-({4-[(1,1-dimethylethyl)oxy]phenyl}methyl)-2-{[(2-methylimidazo[2,1-*b*][1,3]thiazol-6-yl)methyl]amino}-2-oxoethyl)amino] carbonyl}amino)benzoate (**11**)(1.51 g, 77%)

LC/MS (ESI) 592.2 $[M+H]^+$ Rt 1.95 min

2-(Bromomethyl)naphthalene (37.13 mg, 0.168 mmol) was dissolved in CH_3CN (1.5 mL). 1-methylethyl 4-({[((1*S*)-1-({4-[(1,1-dimethylethyl)oxy] phenyl}methyl)-2-{[(2-methylimidazo[2,1-*b*][1,3]thiazol-6-yl)methyl]amino}-2-oxoethyl)amino] carbonyl}amino)benzoate (**11**)(0.05 g, 0.084 mmol) was added. The reaction mixture was heated to 45°C overnight. The reaction mixture was concentrated at reduced pressure. The residue was redissolved in TFA/ CH_2Cl_2 (40%, 15 mL) and stirred at room temperature for 30 mins. The solution was concentrated at reduced pressure. The reaction residue was purified using an Agilent 1100 Series LC with UV and MSD detection and fraction collection. Crude sample was dissolved in a 1:1 mixture of DMSO/methanol (600 uL) for injection onto a ZORBAX Eclipse XDB-C18 column (21.2 x 50 mm) and eluted over ~10 min at a flow rate of 20 mL/min. Fraction collection was triggered by absorption at 230 nm and triggering of the MSD at the MH+ of the desired compound (30.1 mg, 53%).

LC/MS (ESI) 676.6 $[M+H]^+$ Rt 2.47 min

Example 3

Preparation of *N*-[({5-[(cyclohexyloxy)carbonyl]-2-thienyl}amino)carbonyl]-*N*-{[2-methyl-7-(2-naphthalenylmethyl)-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl]methyl}-L-tyrosinamide trifluoroacetate

To 1-(2-methylimidazo[2,1-*b*][1,3]thiazol-6-yl)methanamine **3** (0.90 g, 5.36 mmol) and Boc-Try(t-Bu)-OH (1.98 g, 5.89 mmol) dissolved in DMF (50 mL), o-(7-azabenxotriazol-1-yl)-N,N,N',N'-tetramethyluronium (2.24 g, 5.89 mmol) and diisopropylethyl amine (1.87 mL, 10.72 mmol) were added. After the reaction mixture was stirred at room temperature overnight under argon, the resulting mixture was concentrated under reduced pressure and redissolved with ethyl acetate (100 mL) and water (100 mL). The aqueous phase was extracted with ethyl acetate (75 mLx2). The combined organic phase was washed with water (100 mLx3), brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by combiflash (120 g column, eluting with 2% to 5% MeOH/ CH_2Cl_2) to afford *O*-(1,1-dimethylethyl)-*N*-{[(1,1-dimethylethyl)oxy]carbonyl}-*N*-[(2-methylimidazo[2,1-*b*][1,3]thiazol-6-yl)methyl]-L-tyrosinamide (**12**) (2.01 g, 77%)

LC/MS (ESI) 487.4 $[M+H]^+$ Rt 1.75 min

O-(1,1-dimethylethyl)-*N*-{[(1,1-dimethylethyl)oxy]carbonyl}-*N*-[(2-methylimidazo[2,1-*b*][1,3]thiazol-6-yl)methyl]-L-tyrosinamide (**12**) (100 mg, 0.206 mmol) was dissolved in a mixture of acetonitrile (1.5 mL) and chloroform (1.5 mL). 2-(bromomethyl)naphthalene (68 mg, 0.309 mmol) was added. The reaction solution was heated to 170^{O}C for 20 min via microwave in smith synthesizer. The reaction mixture was concentrated under reduced pressure. The residue was purified by aminopropyl SPE cartridge (10 g column, eluting with 20% to 5% MeOH/ methylenecholoride) to afford *O*-(1,1-dimethylethyl)-*N*-{[(1,1-dimethylethyl)oxy]carbonyl}-*N*-{[2-methyl-7-(2-naphthalenylmethyl)-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl]methyl}-L-tyrosinamide bromide(**13**) (149 mg, 99%)

LC/MS (ESI) 627.6 $[M+H]^+$ Rt 2.24 min

O-(1,1-dimethylethyl)-*N*-{[(1,1-dimethylethyl)oxy]carbonyl}-*N*-{[2-methyl-7-(2-naphthalenylmethyl)-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl]methyl}-L-tyrosinamide bromide(**13**) (191 mg, 0.304 mmol) was dissolved in methylene chloride (6 mL). Trifluoroacetic acid (0.3 mL) was added to the reaction solution dropwise. The reaction mixture was stirred at room temperature for 2 hours and concentrated to afford *N*-{[2-methyl-7-(2-naphthalenylmethyl)-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl]methyl}-L-tyrosinamide trifluoroacetate (**14**) (220 mg, 99%) as a crude product, which was used in the next step without further purification.

LC/MS (ESI) 471.6 $[M+H]^+$ Rt 1.18 min

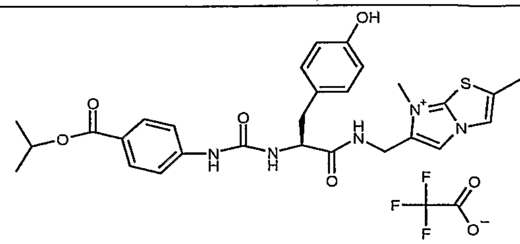
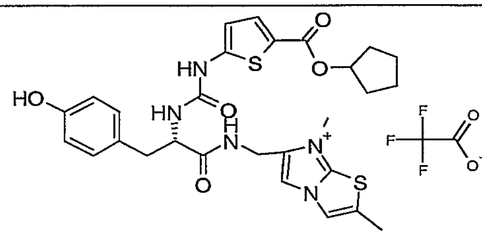
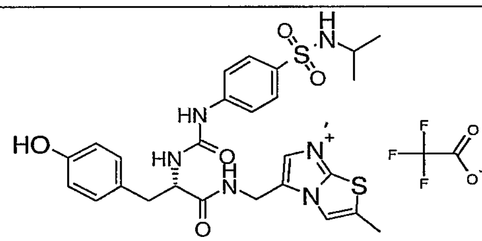
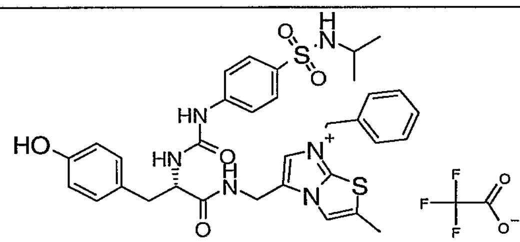
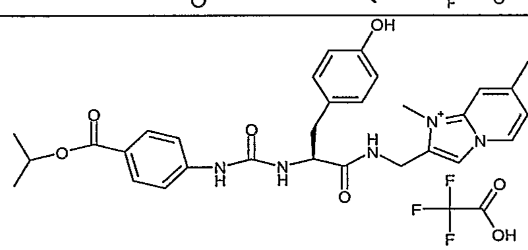
To a mixture of 152 mg (0.675 mmol) cyclohexyl 5-amino-2-thiophenecarboxylate in 5 mL of anhydrous dichloromethane in ice-bath was added 136 mg (0.675 mmol) 4-nitrobezenechloroformate . The reaction mixture was stirred in ice-bath for half an hour and concentrated. Diisopropylethylamine (0.074 mL, 0.424 mmol), *N*-{[2-methyl-7-(2-naphthalenylmethyl)-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl]methyl}-L-tyrosinamide trifluoroacetate (**14**) (100 mg, 0.212 mmol) and dimethyl formamide (5 mL) were added to reaction mixture and stirred overnight. The reaction mixture was concentrated under reduced pressure and purified by reverse phase HPLC (CH_3CN/Water, 0.1 % TFA) to afford the desired product *N*-[({5-[(cyclohexyloxy)carbonyl]-2-thienyl}amino) carbonyl]-*N*-{[2-methyl-7-(2-naphthalenylmethyl)-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl]methyl}-L-tyrosinamide trifluoroacetate (18.6 mg, 13%)

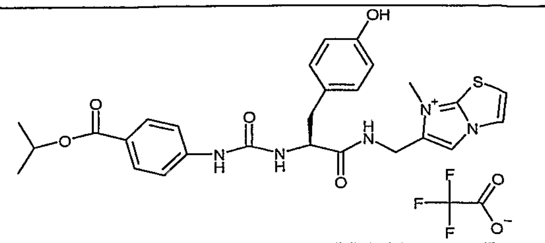
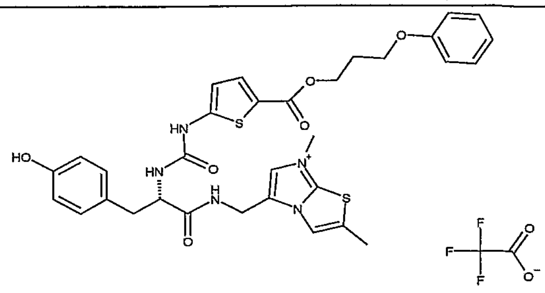
LC/MS (ESI) 722.4 $[M+H]^+$ Rt 2.14 min

Proceeding in a similar manner as described in example **1**, but replacing Cyclohexyl 5-amino-2-thiophenecarboxylate with the appropriate amines, and / or replacing 1-(2-methylimidazo[2,1-*b*][1,3]thiazol-6-yl)methanamine with *N*-methyl-1-(7-

methylimidazo[1,2-*a*]pyridin-2-yl)methanamine or (imidazo[2,1-*b*][1,3]thiazol-6-ylmethyl)aminethe, compounds listed in Tables 1 were prepared.

Table 1

Example	R1	MS $[M]^+$	Rt (min)
4		550.4	1.53
5		582.4	1.71
6		585.4	1.43
7		661.6	1.61
8		544.1	1.58

9		536.0	1.50
10		648.4	1.84

Proceeding in a similar manner as described in example **2**, but replacing 2-(bromomethyl)naphthalene with appropriate substituted benzyl bromide, compounds listed in Tables 2 were prepared.

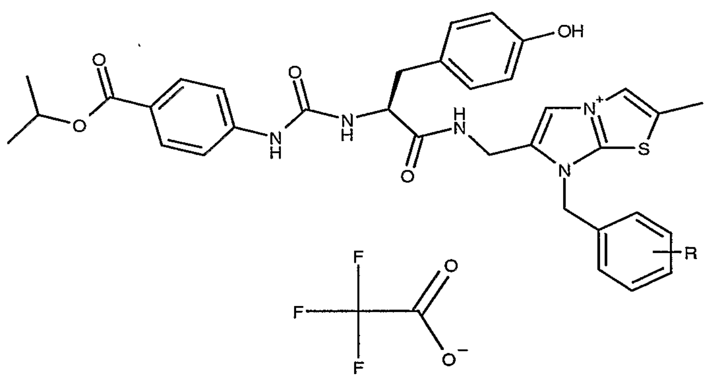


Table 2

Example	R	MS [M]+	Rt (min)
11	2-methyl	640.4	1.93
12	4-bromo	704.4	1.92
13	4-tert-butyl	682.6	2.16
14	4-metyl	640.4	1.98
15	2-fluoro	644.4	1.80
16	3-fluoro	644.4	1.89
17	4-fluoro	644.4	1.85

18	3-trifluoromethyl	694.4	1.97
19	4-trifluoromethyl	694.4	1.94
20	3-cyano	651.4	1.74
21	2-nitro	671.4	1.86
22	3-nitro	671.2	1.82
23	4-nitro	674.4	1.82
24	2-trifluoromethyl	694.4	1.95
25	4-trifluoromethoxyl	710.4	1.98
26	3-trifluoromethoxyl	710.4	1.95
27	3-methoxyl	656.4	1.86

BIOLOGICAL EXAMPLES

The inhibitory effects of compounds at the M_3 mAChR of the present invention are determined by the following *in vitro* and *in vivo* assays:

Analysis of Inhibition of Receptor Activation by Calcium Mobilization:

1) 384-well FLIPR assay

A CHO (chinese hamster ovary) cell line stably expressing the human M3 muscarinic acetylcholine receptor is grown in DMEM plus 10% FBS, 2 mM Glutamine and 200 ug/ml G418. Cells are detached for maintenance and for plating in preparation for assays using either enzymatic or ion chelation methods. The day before the FLIPR (fluorometric imaging plate reader) assay, cells are detached, resuspended, counted, and plated to give 20,000 cells per 384 well in a 50 ul volume. The assay plates are black clear bottom plates, Becton Dickinson catalog number 35 3962. After overnight incubation of plated cells at 37 degrees C in a tissue culture incubator, the assay is run the next day. To run the assay, media are aspirated, and cells are washed with 1x assay buffer (145mM NaCl, 2.5mM KCl, 10mM glucose, 10mM HEPES, 1.2 mM $MgCl_2$, 2.5mM $CaCl_2$, 2.5mM probenecid (pH 7.4.) Cells are then incubated with 50ul of Fluo-3 dye (4uM in assay buffer) for 60 – 90 minutes at 37 degrees C. The calcium- sensitive dye allows cells to exhibit an increase in fluorescence upon response to ligand via release of calcium from intracellular calcium stores. Cells are washed with assay buffer, and then resuspended in 50ul assay buffer prior to use for experiments. Test compounds and antagonists are added in 25 ul volume, and plates are incubated at 37 degrees C for 5 -30 minutes. A

second addition is then made to each well, this time with the agonist challenge, acetylcholine. It is added in 25 ul volume on the FLIPR instrument. Calcium responses are measured by changes in fluorescent units. To measure the activity of inhibitors / antagonists, acetylcholine ligand is added at an EC_{80} concentration, and the antagonist IC_{50} can then be determined using dose response dilution curves. The control antagonist used with M3 is atropine.

2) 96-well FLIPR assay

Stimulation of mAChRs expressed on CHO cells were analyzed by monitoring receptor-activated calcium mobilization as previously described . CHO cells stably expressing M_3 mAChRs were plated in 96 well black wall/clear bottom plates. After 18 to 24 hours, media was aspirated and replaced with 100 µl of load media (EMEM with Earl's salts, 0.1% RIA-grade BSA (Sigma, St. Louis MO), and 4 µM Fluo-3-acetoxymethyl ester fluorescent indicator dye (Fluo-3 AM, Molecular Probes, Eugene, OR) and incubated 1 hr at 37° C. The dye-containing media was then aspirated, replaced with fresh media (without Fluo-3 AM), and cells were incubated for 10 minutes at 37° C. Cells were then washed 3 times and incubated for 10 minutes at 37° C in 100 µl of assay buffer (0.1% gelatin (Sigma), 120 mM NaCl, 4.6 mM KCl, 1 mM KH_2 PO_4, 25 mM NaH CO_3, 1.0 mM $CaCl_2$, 1.1 mM $MgCl_2$, 11 mM glucose, 20mM HEPES (pH 7.4)). 50 µl of compound ($1x10^{-11}$ – $1x10^{-5}$ M final in the assay) was added and the plates were incubated for 10 min. at 37° C. Plates were then placed into a fluorescent light intensity plate reader (FLIPR, Molecular Probes) where the dye loaded cells were exposed to excitation light (488 nm) from a 6 watt argon laser. Cells were activated by adding 50 µl of acetylcholine (0.1-10 nM final), prepared in buffer containing 0.1% BSA, at a rate of 50 µl/sec. Calcium mobilization, monitored as change in cytosolic calcium concentration, was measured as change in 566 nm emission intensity. The change in emission intensity is directly related to cytosolic calcium levels . The emitted fluorescence from all 96 wells is measured simultaneously using a cooled CCD camera. Data points are collected every second. This data was then plotting and analyzed using GraphPad PRISM software.

Methacholine-induced bronchoconstriction

Airway responsiveness to methacholine was determined in awake, unrestrained BalbC mice (*n* = 6 each group). Barometric plethysmography was used to measure enhanced pause (Penh), a unitless measure that has been shown to correlate with the changes in

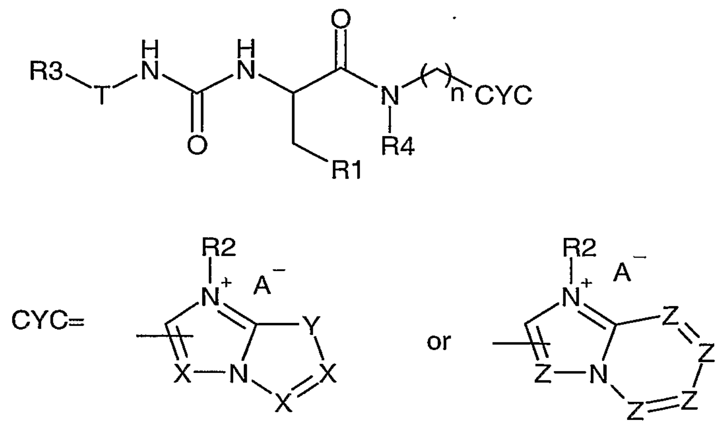
airway resistance that occur during bronchial challenge with methacholine . Mice were pretreated with 50 μl of compound (0.003-10 μg/mouse) in 50 μl of vehicle (10% DMSO) intranasally, and were then placed in the plethysmography chamber. Once in the chamber, the mice were allowed to equilibrate for 10 min before taking a baseline Penh measurement for 5 minutes. Mice were then challenged with an aerosol of methacholine (10 mg/ml) for 2 minutes. Penh was recorded continuously for 7 min starting at the inception of the methacholine aerosol, and continuing for 5 minutes afterward. Data for each mouse were analyzed and plotted by using GraphPad PRISM software.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A compound according to formula (I) below:



(I)

wherein,

Y is S, O; or NR4

X is N, or CR5, provided that the number of N at the X value cannot exceed 2;

Z is N, or CR5, provided that the number of N at the Z value cannot exceed 3;

N is and integer from 0 to 3;

A^- is selected from the group consisting of halo, CF_3COO^-, mesylate, tosylate, and any other pharmaceutically acceptable counter ion;

R1 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, C_3-C_8 alkenyl, unsubstituted or substituted phenyl, or unsubstituted and substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

T is selected from the group consisting of thiophene, furan, thiazole, isothiazole, pyrrole, imidazole, pyrazole and para-substituted phenyl which may be substituted by one or more radical selected from the group consisting of C_1-C_3 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_4 branched or unbranched alkyl, C_3-C_8 cycloalkyl, and C_3-C_8 cycloalkyl lower alkyl or phenyl;

R2 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl and unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group

is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, and C_1-C_3 branched or unbranched alkyl;

R3 is selected from the group consisting of COR6, COOR6, OSO_2R6, $N(R7)SO_2R6$, CONR6R7, NR6R7, OCOR6, OCONR6R7, NHCOR6, N(R7)COR6, NHCOOR6 and NHCONR6R7;

R4 is selected from the group consisting of hydrogen, C1-C3 alkyl and allyl;

R5 is selected from the following group consisting of hydrogen, C1-C3 alkyl, C1-C3 alkenyl, , halo, NR4, OR4, CN, NO_2, and trifluoromethyl;

R6 is selected from the group consisting of substituted or unsubstituted C_1-C_8 branched or unbranched alkyl, C_3-C_{12} cycloalkyl, C_3-C_{12} cycloalkenyl, C_3-C_8 cycloalkyl lower alkyl, C_3-C_8 alkenyl, phenyl, and phenyl C1-C3 lower alkyl wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, nitro, trifluoromethyl, and C_1-C_3 branched or unbranched alkyl; and

R7 is selected from the group consisting of: hydrogen, C1-C4 alkyl and allyl.

2. A compound according to claim 1 wherein:

Y is S, O; or NR4

X is N, or CR5, provided that the number of N at the X value cannot exceed 2;

Z is N, or CR5, provided that the number of N at the Z value cannot exceed 3;

n is an integer from 0 to 3;

A^- is selected from the group consisting of halo, CF_3COO^-, mesylate, tosylate, or any other pharmaceutically acceptable counter ion;

R1 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, C_3-C_8 alkenyl, unsubstituted or substituted phenyl, and unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

T is selected from the group consisting of thiophene, furan, thiazole, isothiazole, pyrrole, imidazole, pyrazole and para-substituted phenyl which may be substituted by radicals selected from the group consisting of C_1-C_3 alkoxy, halo, hydroxy, amino, trifluoromethyl,

C_1-C_4 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl and phenyl;

R2 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl and unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, and C_1-C_3 branched or unbranched alkyl;

R3 is selected from the group consisting of COR6, COOR6, OSO_2R6, $N(R7)SO_2R6$, CONR6R7, NR6R7, OCOR6, OCONR6R7, NHCOR6, N(R7)COR6, NHCOOR6 and NHCONR6R7;

R4 is selected from the group consisting of hydrogen, C1-C3 alkyl and allyl;

R5 is selected from the group consisting of hydrogen, C1-C3 alkyl, C1-C3 alkenyl, , halo, NR4, OR4, CN, NO_2, and trifluoromethyl;

R6 is selected from the group consisting of substituted or unsubstituted C_1-C_8 branched or unbranched alkyl, C_3-C_{12} cycloalkyl, C_3-C_{12} cycloalkenyl, C_3-C_8 cycloalkyl lower alkyl, C_3-C_8 alkenyl, phenyl, and phenyl C1-C3 lower alkyl wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, nitro, trifluoromethyl, and C_1-C_3 branched or unbranched alkyl;

R7 is selected from the group consisting of: hydrogen, C1-C4 alkyl and allyl.

3. A compound according to claim 2 wherein:

Y is S or O;

X is CR5;

Z is CR5;

N is 1 or 2;

A^- is selected from the group consisting of halo, CF_3COO^-, mesylate, tosylate, and any other pharmaceutically acceptable counter ion;

R1 is selected from the group consisting of unsubstituted or substituted phenyl wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

T is selected from the group consisting of thiophene, furan, and para-substituted phenyl which may be substituted by radicals selected from the group consisting of C_1-C_3 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_4 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl and phenyl;
R2 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl and unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, and C_1-C_3 branched or unbranched alkyl;
R3 is selected from the group consisting of COOR6, OSO_2R6, $N(R7)SO_2R6$, and CONR6R7,;
R4 is selected from the group consisting of hydrogen, C1-C3 alkyl and allyl;
R5 is selected from the group consisting of hydrogen, C1-C3 alkyl, C1-C3 alkenyl, , halo, NR4, OR4, CN, NO_2, and trifluoromethyl;
R6 is selected from the group consisting of substituted or unsubstituted C_1-C_8 branched or unbranched alkyl, C_3-C_{12} cycloalkyl, C_3-C_{12} cycloalkenyl, C_3-C_8 cycloalkyl lower alkyl, C_3-C_8 alkenyl, phenyl, or phenyl C1-C3 lower alkyl wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, nitro, trifluoromethyl, and C_1-C_3 branched or unbranched alkyl;
R7 is selected from the group consisting of hydrogen, C1-C3 alkyl and allyl.

4. A compound according to claim 3 wherein:
Y is S;
X is CR5;
Z is CR5;
N is 1;
A^- is selected from the group consisting of halo, CF_3COO^-, mesylate, tosylate, and any other pharmaceutically acceptable counter ion;
R1 is selected from the group consisting of unsubstituted or substituted phenyl wherein, when substituted, a group is substituted at the meta or para position by one radical

selected from the group consisting of C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, nitro, trifluoromethyl, and C_1-C_3 branched or unbranched alkyl;

T is selected from thiophene or para-substituted phenyl;

R2 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl and unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of halo, methoxy, nitro, cyano, trifluoromethyl, and C_1-C_2 alkyl;

R3 is selected from the group consisting of COOR6, OSO_2R6, and $N(R7)SO_2R6$;

R4 is hydrogen;

R5 is hydrogen;

R6 is selected from the group consisting of substituted or unsubstituted C_1-C_8 branched or unbranched alkyl, C_3-C_9 cycloalkyl, C_3-C_9 cycloalkenyl, C_3-C_8 cycloalkylmethyl, and C_3-C_8 alkenyl;

5. A compound according to claim 4 selected from the group consisting of:

N-[({5-[(cyclopentyloxy)carbonyl]-2-thienyl}amino)carbonyl]-*N*-[(2,7-dimethylimidazo[2,1-*b*][1,3]thiazol-7-ium-6-yl)methyl]-L-tyrosinamide trifluoroacetate;

N-[({5-[(cyclohexyloxy)carbonyl]-2-thienyl}amino)carbonyl]-*N*-[(2,7-dimethylimidazo[2,1-*b*][1,3]thiazol-7-ium-6-yl)methyl]-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)amino]sulfonyl}phenyl)amino]carbonyl}-*N*-{[2-methyl-7-(phenylmethyl)imidazo[2,1-*b*][1,3]thiazol-7-ium-6-yl]methyl}-L-tyrosinamide trifluoroacetate;

N-[(2,7-dimethylimidazo[2,1-*b*][1,3]thiazol-7-ium-6-yl)methyl]-*N*-{[(4-{[(1-methylethyl)amino]sulfonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

4-[(2*S*)-3-{[(1,7-dimethylimidazo[1,2-*a*]pyridin-1-ium-2-yl)methyl]amino}-2-({[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}amino)-3-oxopropyl]benzenolate trifluoroacetate;

N-[({5-[(cyclohexyloxy)carbonyl]-2-thienyl}amino)carbonyl]-*N*-{[2-methyl-7-(2-naphthalenylmethyl)-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl]methyl}-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-[(7-methylimidazo[2,1-*b*][1,3]thiazol-7-ium-6-yl)methyl]-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-[(7-methylimidazo[2,1-*b*][1,3]thiazol-7-ium-6-yl)methyl]-L-tyrosinamide trifluoroacetate;

N-[(2,7-dimethylimidazo[2,1-*b*][1,3]thiazol-7-ium-6-yl)methyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-({2-methyl-7-[(2-methylphenyl)methyl]-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-L-tyrosinamide trifluoroacetate;

N-({7-[(4-bromophenyl)methyl]-2-methyl-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino] carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(7-{[4-(1,1-dimethylethyl)phenyl]methyl}-2-methyl-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl)methyl]-*N*-{[(4-{[(1-methylethyl)oxy] carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-({2-methyl-7-[(4-methylphenyl)methyl]-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-L-tyrosinamide trifluoroacetate;

N-({7-[(2-fluorophenyl)methyl]-2-methyl-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino] carbonyl}-L-tyrosinamide trifluoroacetate;

N-({7-[(3-fluorophenyl)methyl]-2-methyl-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino] carbonyl}-L-tyrosinamide trifluoroacetate;

N-({7-[(4-fluorophenyl)methyl]-2-methyl-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino] carbonyl}-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-[(2-methyl-7-{[3-(trifluoromethyl)phenyl]methyl}-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl)methyl]-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-[(2-methyl-7-{[4-(trifluoromethyl)phenyl]methyl}-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl)methyl]-L-tyrosinamide trifluoroacetate;

N-({7-[(3-cyanophenyl)methyl]-2-methyl-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino] carbonyl}-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-{[2-methyl-7-(2-naphthalenylmethyl)-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl]methyl}-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-({2-methyl-7-[(2-nitrophenyl)methyl]-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-({2-methyl-7-[(3-nitrophenyl)methyl]-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-({2-methyl-7-[(4-nitrophenyl)methyl]-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl}methyl)-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-[(2-methyl-7-{[2-(trifluoromethyl)phenyl]methyl}-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl)methyl]-L-tyrosinamide trifluoroacetate;

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-{[2-methyl-7-({4-[(trifluoromethyl)oxy]phenyl}methyl)-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl]methyl}-L-tyrosinamide trifluoroacetate

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl);amino]carbonyl}-*N*-{[2-methyl-7-({3-[(trifluoromethyl)oxy]phenyl}methyl)-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl]methyl}-L-tyrosinamide trifluoroacetate;

N-[(2,7-dimethylimidazo[2,1-*b*][1,3]thiazol-7-ium-5-yl)methyl]-*N*-({[5-({[3-(phenyloxy)propyl]oxy}carbonyl)-2-thienyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate; and

N-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-*N*-[(2-methyl-7-{[3-(methyloxy)phenyl]methyl}-7*H*-imidazo[2,1-*b*][1,3]thiazol-4-ium-6-yl)methyl]-L-tyrosinamide trifluoroacetate; or a pharmaceutically acceptable salt.

6. A pharmaceutical composition for the treatment of muscarinic acetylcholine receptor mediated diseases comprising a compound according to claim 1 and a pharmaceutically acceptable carrier thereof.

7. A method of inhibiting the binding of acetylcholine to its receptors in a mammal in need thereof comprising administering a safe and effective amount of a compound according to claim 1.

8. A method of treating a muscarinic acetylcholine receptor mediated disease, wherein acetylcholine binds to said receptor, comprising administering a safe and effective amount of a compound according to claim 1.

9. A method according to claim 8 wherein the disease is selected from the group consisting of chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema and allergic rhinitis.

10. A method according to claim 8 wherein administration is via inhalation via the mouth or nose.

11. A method according to claim 8 wherein administration is via a medicament dispenser selected from a reservoir dry powder inhaler, a multi-dose dry powder inhaler or a metered dose inhaler.

12. A method according to claim 11 wherein the compound has a duration of action of 24 hours or more.

13. A method according to claim 12 wherein the compound has a duration of action of 36 hours or more.